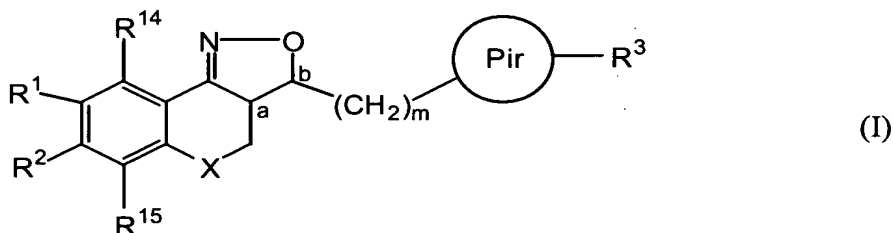


ABSTRACT

C6- AND C9-SUBSTITUTED ISOXAZOLINE DERIVATIVES
AND THEIR USE AS ANTI-DEPRESSANTS

The invention concerns substituted tricyclic isoxazoline derivatives, more in particular tricyclic dihydrobenzopyranoisoxazoline, dihydroquinolinoisoxazoline, dihydronaphthalenoisoxazoline and dihydrobenzothiopyranoisoxazoline derivatives substituted on at least one of the C6- and C9-positions of the phenylpart of the tricyclic moiety with a selected radical, according to Formula (I)



wherein $X = CH_2, N-R^7, S$ or O , R^1, R^2, R^{14} and R^{15} are certain specific substituents, with the proviso that at least one of R^{14} and R^{15} is not hydrogen, Pir is preferably an optionally substituted piperidinyl or piperazinyl radical and R^3 represents an optionally substituted aromatic homocyclic or heterocyclic ring system including a partially or completely hydrogenated hydrocarbon chain of maximum 6 atoms long with which the ring system is attached to the Pir radical and which may contain one or more heteroatoms selected from the group of O, N and S ; a process for their preparation, pharmaceutical compositions comprising them and their use as a medicine, in particular for the treatment of depression, anxiety, movement disorders, psychosis, Parkinson's disease and body weight disorders.. The compounds according to the invention have surprisingly been shown to have a serotonin (5-HT) reuptake inhibitor activity in combination with additional α_2 -adrenoceptor antagonist activity and show a strong anti-depressant activity without being sedative. The invention also relates to novel combination of isoxazoline derivatives according to the invention with one or more other compounds selected from the group of antidepressants, anxiolytics, anti-psychotics and anti-Parkinson's disease drugs to improve efficacy and/or onset of action.